REMARKS

With the present amendment, claims 1-8, 10, 12, 14-22, and 62 remain pending. Claim 1 is amended to recite the limitations of currently canceled claims 11, 13, and 61. Claim 1 is further amended to recite the step of dissolving one or more phospholipids and one or more sterols in a solvent or mixture of solvents as well as the step of removing the solvent or mixture of solvents before or after hydrating the lipids. Support for this claim amendment can be found in at least paragraphs [0016], [0018]; [0022], and [0045] of the published application.

In addition, claim 1 has been amended to clarify that the novel claimed process produces novel non-pegylated liposomes that have a blood circulation half life of at least 25 times longer than conventional non-liposomal formulations. Support for this claim amendment can be found in paragraph [0065] of the published application.

In claim 62, the term "size" is amended to read as "sized." The step of removing the solvent before or after hydrating the lipid film is removed as it was incorporated into claim 1.

Accordingly, no new matter is being added through these claim amendments.

Claims 9, 23-60 were previously canceled. Claims 11, 13 and 61 are canceled with the current amendment. Applicants reserve the right to pursue the canceled claims through one or more divisional applications. Reconsideration in view of the above amendments and following remarks is respectfully requested.

Interview summary

A telephonic interview was held on January 15, 2008 with applicants' representative, Teresa Lavenue and Examiner Gollamudi S. Kishore. Applicants' representative had requested the Examiner's supervisor to be present but Examiner Kishore denied this request noting that he does not have his supervisor present during Interviews.

All the pending claims were discussed with emphasis on claim 1. No agreements regarding claim amendments were reached. No exhibits were presented. The Kirpotin reference was discussed with regard to obviousness rejections. Applicants disagree with the Examiner's characterization that the hydration medium is critical. Applicants note that is one of the elements and not the only element. The Examiner suggested running tests comparing liposomes made by the recited method with that of Kirpotin and also suggested running tests with different amounts

of hydration buffer. Applicants also reiterated that Kirpotin does not teach all of the claimed elements, such as non-pegylated liposomes made with a certain amount of hydration buffer that were long circulating. In response, the Examiner suggested that a claim limitation be entered into the claim more clearly defining the term long circulating.

Claim Rejections - 35 U.S.C § 112, second paragraph

The Examiner has rejected claim 61 under 35 U.S.C § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner contends that claim 61 is inconsistent with claim 1.

With the current amendment, Applicants cancel claim 61 and incorporate the limitations of claim 61 into claim 1. Applicants respectfully submit that, in light of the present amendment, the rejection under 35 U.S.C § 112, second paragraph is overcome and should be withdrawn.

Claim Rejections - 35 U.S.C § 103(a)-Kirpotin

The Examiner maintains the rejection of claims 1-8, 10-22 and 61 under 35 U.S.C § 103(a) as being unpatentable over Kirpotin (U.S. Patent No. 6,110,491). Applicants submit that Kirpotin does not teach or suggest all of the claim limitations.

Prima facie Case of Nonobviousness Not Established

Applicants respectfully contend that the Examiner has failed to establish a *prima facie* case of nonobviousness because: (1) Kirpotin simply does not teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in currently amended claim 1; and (2) no one would be motivated (no reasonable expectation of success shown) to even consider Kirpotin for suggesting a long circulating non-pegylated liposome made by the process of claim 1.

The Examiner states that "Kirpotin discloses a method of preparation of liposomes by forming a lipid film and hydrating it with a buffer containing ammonium sulfate (Example 7)." See page 2, line 22 – page 3, line 1 of the Office Action dated January 22, 2008. Applicants submit that Example 7 sets forth a method of loading doxorubicin into a liposome but fails to teach or suggest the method of claim 1. Specifically, Kirpotin's Example 7 does not disclose a

method of preparation of liposomes by forming a lipid film and hydrating it with a buffer containing ammonium sulfate as contended by the Examiner. Instead, Example 7 states:

> Liposomes with entrapped ammonium sulphate or ammonium polyacrylate were prepared from the lipid mixture of from the lipid mixture of hydrogenated soybean phosphatidylcholine (Avanti PolarLipids, Ala., U.S.A.), cholesterol (Calbiochem, USA), and poly(ethylene glycol) (Mol. weight 2,000) derivative of distearoyl phosphatidyl ethanolamine (PEG-DSPE) (Sygena, Switzerland), at the molar ratio 60:40:6, by lipid film hydration, repetitive freezing-thawing at 60°C (6 times) and extrusion through two stacked polycarbonate track-etched membranes with the pore size 100 nm at 60°C (12 times).

See column 14, lines 17-24. Thus, Example 7 does not teach or suggest using the hydration media composition recited in claim 1. There is simply nothing about what hydration media Kirpotin used in this Example. All the reader knows is that the liposomes had entrapped ammonium sulfate or ammonium polyacrylate. There is nothing in Kirpotin relating to a teaching or suggestion that Kirpotin used a hydration medium comprising ammonium sulfate and sucrose, either in an inner buffer (hydration media used for hydrating phospholipids and sterols) or in an outer buffer used with liposomes. It may also be noted that there is no motivation to use an outer buffer as an inner buffer as the functions of these two buffers are different. Further, in Example 7 of Kirpotin it is not necessary to have ammonium sulphate in hydration buffer for entrapping it in the liposome as ammonium sulphate may be entrapped even after the liposomes are formed.

In addition, as argued in the previous response, nowhere does Kirpotin teach or suggest making long circulating (wherein the non-pegylated liposomes have a blood circulation half life of at least 25 times longer than conventional non-liposomal formulations when tested in Swiss albino mice at equivalent doses) non-pegylated liposomes. In addition, Example 7 clearly shows that these liposomes were made with pegylated phospholipids.

Next, the Examiner states that "Kirpotin also teaches that if necessary, to achieve an osmolarity of 377 mmole/kg, sucrose could be added to the medium (Example 8)." See page 3, lines 1-3 of the Office Action dated January 22, 2008. First, in Example 8, the buffer being described is a loading buffer. Kirpotin's invention relates to loading buffers and the use of an ammonium sulfate gradient to achieve an allegedly higher loading capacity. The fact that Kirpotin teaches using sucrose in the loading buffer to raise osmolarity in the loading buffer has

no bearing on the medium used to hydrate the phospholipids and sterols (hereinafter referred to as just phospholipids). Thus, applicants submit that Kirpotin does not teach in Example 8 (as well as in the rest of the patent) the use of an aqueous hydration media comprising ammonium sulfate and sucrose to hydrate phospholipids to make non-pegylated liposomes, let alone teach or suggest the recited ratio of hydration media to recited phospholipids.

The Examiner dismisses Applicants' arguments presented in the previous response as well as Mr. Pai's Declaration regarding the fact that Kirpotin does not teach or suggest a process for manufacture of non-pegylated liposomes. Applicants again point out that there is simply no teaching or suggesting how to make long circulating non-pegylated liposomes. Every example in Kirpotin teaches the use of pegylated phospholipids in the process of making the liposomes. There is nothing in Kirpotin that even suggests to one skilled in the art to make non-pegylated liposomes. The Examiner concedes that the examples in Kirpotin use pegylated phospholipids, however the Examiner points to column 9, lines 22-23 to support his contention that although Kirpotin uses pegylated phospholipids, the fact that the specification notes that naturally occurring or synthetic phospholipids can be used implies the use of pegylated phospholipids is not necessary. This is pure hindsight reasoning at its best. The Examiner reaches this conclusion without providing any evidentiary basis or scientific principle in support of his conclusion. Naturally occurring and synthetic phospholipids could be used to make liposomes with pegylated phospholipids. There is nothing in Kirpotin that would lead one to believe that the language on col. 9, lines 22-23 teach not using pegylated in the manufacture of liposomes. This particular sentence says ". . . prepared from conventional vesicle forming lipids." Applicants respectfully submit that one skilled in the art would understand that conventional vesicle forming lipids also include pegylated phospholipids.

A more reasonable interpretation when reading Kirpotin as a whole and not using hindsight argumentation, would believe that this passage implies only that one could use synthetic or naturally occurring phospholipids, which one could use along with pegylated phospholipids as shown in column 9, (which also discusses the use of polymers in hydration medium). Since all of the examples teach using pegylated phospholipids, one would assume that pegylated phospholipids would be added to synthetic or naturally occurring phospholipids. In fact, the very next paragraph in the specification goes on to mention the use of pegylated

phospholipids. The only way the Examiner could read this sentence to arrive at the conclusion that it teaches making non-pegylated liposomes according to the currently claimed methods (i.e. ammonium sulfate and sucrose aqueous hydration media, certain ratio of hydration media to phospholipid, etc.) can only come from hindsight analysis, especially when every single example in Kirpotin teaches using pegylated phospholipids in the liposome manufacture.

Further, by relying only on the cited passage of Kirpotin regarding the use of synthetic and naturally occurring phospholipids, the Examiner has failed to properly consider Kirpotin for everything it teaches. The predecessor to the Federal Circuit has explicitly held:

> It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciate of what such reference fairly suggest to one of ordinary skill in the art.

In re Wesslau, 353 F.2d 238, 241 (CCPA 1965).

Thus, when properly viewed in its entirety, Kirpotin does not render the pending claims obvious because Kirpotin does not teach or even suggest non-pegylated liposomes. To simply conclude that the teachings of Kirpotin with regard to the preparation of pegylated liposomes renders the pending claims obvious represents improper consideration of Kirpotin in its entirety and impermissible hindsight.

The Examiner concedes that Kirpotin does not teach the claimed amount of aqueous hydration medium per mol of phospholipid. However, the Examiner than makes a leap and totally ignores the submitted Declaration and says that that "it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results." (emphasis added).

Applicants submit that this statement again shows that the Examiner has used impermissible hindsight in his reasoning and analysis. To what "best possible results" is the Examiner referring? What caused him to look to obtaining this result, if not the present application? Since Kirpotin relates to achieving a higher loading of liposomes, where is the Examiner coming up with the idea that one would be motivated to take Kirpotin (or any other reference for that matter) to alter amounts of hydration medium, use ammonium sulfate and sucrose in the hydration medium, with the recited phospholipids and not use pegylated

phospholipids to achieve a long circulating liposome? If anything, after reading Kirpotin, one would be motivated to figure out an improved loading efficiency, not how to achieve a long circulating liposome using non-pegylated phospholipids. As discussed above and in previous responses, Kirpotin does not even relate to long circulating liposomes, so surely this motivation is not coming from Kirpotin. Rather applicants submit that this motivation has been fabricated by the Examiner with the knowledge of the present invention to find "motivation" – pure classical hindsight reasoning. Where does Kirpotin or any other art for that matter suggest to use the recited ratio of hydration media to phosphopolipids to achieve a long circulating non-pegylated liposome? Where is there motivation or any hint of a reasonable expectation of success? Why would one be motivated to choose a certain ratio? To what end would one be motivated to choose this ratio and remove the use of pegylated phospholipids? All of this comes from the present application and not from the cited prior art and hence is impermissible hindsight reasoning.

Further, Kirpotin simply does not show, predict or even hint that one could reduce the amount of hydration media to the recited range to allow one to make a long-circulating stable liposome without using pegylated phospholipids. Such a result could not be predicted based on common knowledge or by one of ordinary skill, especially in light of the unpredictable nature of the biotechnological arts. As a matter of act, applicants submit that a person skilled in the art would expect a shorter circulation when non-pegylated phospholipids are used. See paragraph [0013] of the published present pending application.

In summary, the Examiner has failed to bear the initial burden of establishing a *prima facie* case of nonobviousness. Kirpotin does not teach or suggest all of the claimed elements of the presently amended claims. Accordingly, applicants request withdrawal of this ground of rejection.

Evidence of Unexpected Results Must Be Weighed

The Examiner alleges that "in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amount of the hydrating medium to obtain the best possible results." See page 3, lines 8-12 of the Office Action dated January 22, 2008. In reference to the Declaration of Mr. Pai (referred to as the Declaration of Mr. Annappa by the

Examiner) dated October 18, 2007, the Examiner contends the "arguments are not persuasive since the proper comparison to show unexpected results would be the comparison with Kirpotin and not with the commercially available pegylated product since this product was not used in the rejection." See page 4, lines 1-4 of the Office Action dated January 22, 2008. Applicants respectfully submit that the Examiner has failed to properly consider the Declaration of Mr. Pai dated October 18, 2007.

Assuming, *arguendo*, the Examiner previously established a *prima facie* case of obviousness, Applicant previously rebutted such a *prima facie* case by providing a "showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984). This showing was fully presented in the Declaration of Mr. Pai dated October 18, 2007. The method of claim 1 increases circulation time of liposomes and reduces toxicity, thus avoiding the use of any polymer or pegylated phospholipids, which has been shown to cause a different type of toxicity-(Hand-Foot-Syndrome). At the time of the Kirpotin patent and until the time of instant invention, the use of a polymer was necessary for increasing circulation time of liposomes and reducing toxicity of the drug entrapped in it.

The present invention also unexpectedly shows long circulation time and reduced toxicity of Doxorubicin compared to prior art. See paragraph [0095] of the published application and Table I- Example II, and Declaration of Mr. Pai, paragraph 8, 9 and 10. Mr. Pai in his Declaration has shown that reduction in hydration volume leads to good results (longer circulation time and reduced toxicity). The Examiner has provided no prior art, in the field of liposomes, pegylated or otherwise, that teaches or suggest the relation between reduction in hydration volume and the reduction in toxicity and the increase in circulation time. The Examiner has provided no prior art teaching or suggesting that a reduction in the volume of hydration medium is linked or shown to be related to increasing the circulating time of liposomes.

The filed application notes that pegylation was used for achieving long circulation because the same process was not giving long circulation without the use of pegylated phospholipids. However, after its' use, it was found that it leads to "Hand Foot Syndrome." See para. [0013] of the published application. The present invention gets rid of this "Hand Foot Syndrome" by making non-pegylated liposomes, which thus avoids the cause of the "Hand Foot

Syndrome" toxicity itself and at the same time increases the long circulation period that is desirable, and is what pegylation tried to achieve.

The Examiner avoids proper consideration of the Declaration of Mr. Pai by contending the comparison with the commercial embodiment, CAELYX, was improper. Since the Kipotin liposomes are pegylated, a comparison with a market product that is also pegylated is proper. The comparison is meant to distinguish between the cited prior art (a pegylated liposome) from the product of the claimed method (a non-pegylated liposome). Thus, the comparison with CAELYX, a commercially available pegylated liposome, however, was proper to show unexpected results because the closest prior art need not be a reference relied upon by the Examiner. See *In re Holladay,* 584 F.2d 384, 199 USPQ 516 (CCPA 1978). The fact that CAELYX is a commercial product is not prejudicial to comparison with the claimed invention. In fact, the CCPA has held that "[i]t is quite conceivable that the commercial standard would be less expensive to make but, at the same time, less effective, so that test results involving it would be favorable . . . ." See *In re Wright,* 569 F.2d 1124, 1128, 193 USPQ 332, 336 (CCPA 1976). Thus, the unexpected results articulated in the declaration of Mr. Pai are not only appropriate for consideration and comparison but properly illustrate that one of ordinary skill would not expect that by simply reducing the amount of hydration buffer, in the selected phospholipids and selected hydration media composition in given proportions one would obtain a stable liposome without the need for using pegylated phospholipids. Applicants further note that industrial application is an important criteria of patentability, and as such comparison with industrially produced and marketed product is most relevant.

Accordingly, applicants request reconsideration and withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Kirpotin/Emanuel

The Examiner rejects claim 62 under 35 U.S.C §103(a) as being unpatentable over Kirpotin in view of Emanuel (US2002/0151508). As discussed above, Kirpotin fails to teach or suggest all of the claimed limitation in claims 1-8, 10-22 and 61. Emanuel fails to cure these deficiencies. Further, Emanuel like Kirpotin teaches the use of pegylated liposomes. Emanuel teaches a method of treating a proliferative disease comprising administering a liposomal

anthracycline composition, which is pegylated liposomal doxorubicin. In addition, Emanuel does not disclose or teach how the liposomal anthracycline composition is prepared. While Emanuel discloses the use of histidine and sucrose, Emanuel fails to teach or suggest using a sucrose-histidine buffer solution for removing extra liposomal hydration salt for forming non-pegylated sized liposomes (of claim 62).

In Emanuel, histidine and sucrose are part of pegylated liposomes. The former is used for buffer action and the later for isotonicity. (See Emanuel [0010] – [0015] and [0033]). In Emanuel, there is no teaching or suggestion of using a sucrose-histidine buffer in the process of making liposomes, and in concentrations as in the instant invention. These may be individually loaded during preparation of liposomes, and it is incorrect to say that Emanuel shows its routine use.

In addition, the Examiner has failed to point to any motivation or suggestion that a person of ordinary skill would have even looked to Emanuel to accomplish a reduction in toxicity or increase in circulation time without any pegylated phospholipid such as MPEG-DSPE (See [0012]) that is used in Emanuel. Further, Emanuel does not teach or suggest any process of making of liposomes, wherein a sucrose-histidine buffer is used for removing extra liposomal hydration salt from liposomal composition to form non-PEGylated sized liposomes as recited in claim 62. Emanuel does not show any reduction in toxicity of Doxorubicin and no increase in circulation time of liposomes using pegylated liposomes nor would have one of ordinary skill even considered Emanuel helpful to solve such a problem.

Accordingly, applicants request reconsideration and withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Forssen/Janoff

The Examiner rejects claims 1-8, 10-22 and 61-62 under 35 U.S.C §103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635).

First, the abstract of Janoff provides the gist of the Janoff process. The very first sentence is: *"Dehydrated liposomes are prepared by drying liposome preparations under reduced pressure in the presence of one or more protective sugars, e.g., the disaccharides, trehalose and sucrose."* This indicates that Janoff does not disclose hydration of phospholipids

to form liposomes using sugar in the hydration medium as Janoff is concerned with rehydrating dehydrated liposomes. Protective sugars are used while drying liposome preparations under reduced pressure. Further the protective sugar can be omitted if: (1) the liposomes are the type which have multiple lipid layers; (2) the dehydration is preferred without prior freezing; and (3) the dehydration is performed to an end point that results in sufficient water left in the preparation (e.g. at least 12 moles water/mole lipid). In the process of claim 1 of the present application, at the stage of hydration of phopholipids, all the three conditions exists and thus, according to Janoff, addition of sugar is not necessary.

Second, Janoff's hydration medium for hydrating dehydrated liposomes contains NaCl and HEPES containing sugar. In contrast, the claimed hydration medium contains ammonium sulfate and sucrose for hydrating phospholipids. Applicants submit that the use of NaCl and Hepes does not teach or suggest the use of ammonium sulfate and sucrose in the method of hydration of phospholipids. The Examiner provides no reason why one of ordinary skill in the art would have been motivated to look to a reference that teaches NaCl and HEPES for hydrating dehydrated liposomes to arrive at using ammonium sulfate for hydrating phospholipids. Further, the use of a hydration medium is not independent of the quality of the hydration medium's composition. How does the Examiner make the leap that a reference teaching NaCl/Hepes/sugar rehydration buffer used to rehydrate dehydrated liposomes teaches or suggests ammonium sulfate/sucrose hydration buffer used to hydrate phopholipids at the recited ratio? Applicants contend that such a stark difference in the composition and the reasons for use of the Janoff medium and the hydration medium of the present invention further illustrates why one of ordinary skill would have never even considered Janoff, much less be motivated by Janoff to combine its teachings as suggested by the Examiner to arrive at a process of preparing liposomes as recited in claim 1 (i.e., a process of preparing long circulating liposomes, incorporating ammonium sulfate and sucrose in limited defined amounts of hydration medium).

Third, Janoff teaches liposomes that are required to be dehydrated and then rehydrated to achieve long-term storage without substantial loss of their internal contents. Janoff does not teach or suggest that the addition of sugar in the hydration media along with ammonium sulfate for hydrating phospholipids in the preparation of liposomes is required (as required by the

present claims), in a certain ratio and in combination with the recited phosphatidyl cholines to achieve a long-circulating liposome.

Fourth, applicants submit that Janoff does not even teach using sucrose in a hydration buffer when dehydration/rehydration is not necessary. Put another way, one of ordinary skill would not have been motivated to even consider using just one of these recited elements (i.e. use of sucrose with ammonium sulfate in the hydration buffer) in the Janoff process because, according to Janoff, when there is no dehydration step (as in the present pending claim 1), there is no need for rehydration and therefore no need for a protective sugar. See Janoff abstract stating how much dehydration is necessary to incorporate sugar in the rehydration medium for rehydration of dehydrated liposomes. Thus, the method of hydration of phospholipids using sucrose in the medium to create liposome is not at all obvious from Janoff. In this way, Janoff effectively teaches away from the use of sugar in the hydration medium when dehydration is not necessary, as is the case in claim 1, where the liposomes formed are in abundant water. Janoff does not teach or suggest all the elements of the present claims nor teach the liposome produced by the claimed method.

Next, the Examiner contends that although Forssen does not specifically teach the amount aqueous medium added per mole of phospholipids, it is allegedly obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results. First, similar to Janoff, Forssen does not teach or suggest all of the elements of the claim nor teach the liposome produced by the claimed method. So even if the claimed ratio of hydration media was taught or suggested by Forssen, the combination of these two references do not teach or suggest the claimed invention. The Examiner further contends that one of ordinary skill in the art would allegedly be motivated to use claimed amounts of aqueous medium with the expectation of obtaining similar results since Janoff teaches such a hydration amount. This statement by the Examiner means that the motivation to have a hydration buffer of ammonium sulfate and sucrose is assumed based on Janoff. As established above, no such teaching or suggestion nor motivation exists.

With respect to claim 62, the Examiner states that "[t]he criticality of the histidine buffer in claim 62 is not readily apparent to the examiner in the absence of comparative studies." The unexpected and exceptional reduction in toxicity and increase in circulation time observed by

liposomes produced by the process of claim 1 is a concerted effect of all steps recited in claim 1. Claim 1 recites a patentable process. Claim 62 depends from claim 1 and further defines "removing extra-liposomal hydration salt from the liposomal composition using sucrose-histidine buffer solution." The Examiner attempts to isolate the criticality of amount of buffer without considering the relevancy of the liposomal composition and phospholipid composition. The sucrose-histidine buffer solution is used to remove extraliposomal hydration media. Therefore, the sucrose-histidine buffer solution is related to the hydration media quality, quantity, as well as the quality of liposomes, which is also a function of lipid composition. As such, Applicants submit that these references do not teach or suggest all of the elements of the pending claims and as such requests withdrawal of this ground of rejection.

Next, the Examiner relies on the teachings of Maruyama and Park to support the contention that Applicant has not shown that because of hydration buffer amounts, the liposomes have longer circulating time. Maruyama shows that the extent of prolongation of circulation time of liposome compositions is related to the amount and degree of polymerization of polyglycerides in dipalmitoylphosphatidylpolyglycerol. Maruyama's teaching regarding the prolongation of circulation time relies on negatively charged entities like phosphatidyl glycerols (PG), phosphatidyl serine (PS) or pegylated entities or any polymer in hydration medium, each of which are not relied upon or recited in the process of claim 1 as currently amended. Amended claim 1 recites only certain phosphatidyl cholines. As supported by the specification and reiterated in the Declaration of Mr. Pai, the prolongation of circulation time is obtained by reduction in hydration volume as opposed to incorporation of negatively charged entities.

The Park paper teaches liposome compositions including dioleoylphosphatidyl ethanolamine (DOPE) derivatives made by coupling dicarboxylic acids. As explained above, the instant invention is not concerned with such negatively charged phospholipids nor their shielding by bulky sugar moieties. Thus, Park and Maruyama are not only irrelevant to the current process but one of ordinary skill in the art would not have even considered or been motivated to rely on the teachings of Park and Maruyama.

Next, the Examiner contends that the word "comprising" in claim 1 does not exclude further dehydration and rehydration as allegedly taught by Janoff. The specification of the instant application nowhere mentions dehydration or rehydration of liposomes in the claimed

method of manufacture. However, Janoff is primarily concerned with using sugars to protect the liposomes during hydration and rehydration of the liposomes and nowhere teaches the use of a sucrose-histidine solution to remove salt. Thus, there is no teaching or suggestion to use a sucrose-histidine buffer to remove extra liposomal salt in the liposomal composition as in pending claim 62. Using a sugar for one purpose in a liposome reference does not suggest, let alone teach, the use of a sugar for another purpose just because both references concern liposomes. In fact, Janoff uses hydration media to rehydrate dehydrated liposomes and the instant invention hydration medium is hydrating phospholipids to form liposomes; it does not hydrate dehydrated-liposomes. This is akin to finding the use of baking soda to clean an oven in a kitchen obvious in light of using baking soda in the refrigerator to absorb odors. Both use baking soda in the kitchen, but the purpose for each is so different that one would not suggest the other just because both uses are in the kitchen. Similarly, just because Janoff teaches using a sugar in liposomes to provide protection during dehydration or rehydration does not teach or suggest the use of a histidine-sugar solution to remove salt.

As such, Applicants respectfully submit that Forssen and Janoff, alone or in combination, do not teach or suggest each and every element of the claims and accordingly requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Forssen/Janoff/Emanuel

The Examiner rejects claim 62 under 35 U.S.C §103(a) as being unpatentable over Forssen in combination with Janoff, in further view of Emanuel. As articulated above, Forssen and Janoff, alone or in combination, do not teach or suggest each and every element of the claims. Emanuel fails to cure the shortcomings of Forssen and Janoff. Specifically, Emanuel fails to teach or suggest the sucrose-histidine buffer of claim 62 much less certain other claim elements, such as nonpegylated liposomes, and the ratio of hydration media to phospholipids. The Examiner has also failed to point to any motivation or reasonable expectation of success as to why a person of ordinary skill would have even looked to Emanuel to accomplish a reduction in toxicity or increase in circulation time without any pegylated phospholipid such as MPEG-DSPE.

Accordingly, Applicant respectfully requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Forssen/Janoff/Radhakrishnan/Uchiyama

The Examiner rejects claims 1-8, 10-22 and 61-62 under 35 U.S.C §103(a) as being unpatentable over Forssen in combination with Janoff, further in view of Radhakrishnan or Uchiyama.

As discussed above, neither Forssen nor Janoffl, nor their combination, teach or suggest all of the recited claimed elements of the rejected claims. These additional references do not cure these deficiencies. Radhakrishnan generally discloses a method for delivering a therapeutic dosage of corticosteroid drug to the lungs, for treating a lung condition or disease. See Abstract of Radhakrishnan. An aqueous suspension of sized liposomes containing the drug in liposome-entrapped form is aerosolized under conditions which produce aerosol particle sizes favoring particle deposition in a selected region of the respiratory tract, and the aerosol is administered in an amount which delivers the therapeutic dosage level to the selected lung region. See Abstract of Radhakrishnan.

The composition of phospholipids and hydration medium recited in claim 1 are quite different from the phospholipids and hydration medium taught by Radhakrishnan. More specifically, Radhakrishnan teaches the use of EPG as a phospholipid component. See column 5, lines 5-29; see Example 1. Radhakrishnan also teaches a process whereby the drug is taken up with lipids in the solvent. See column 5, lines 5-29; see Example 1. The hydration medium is simply phosphate buffered saline. See column 5, lines 5-29; see Example 1. None of these aspects are recited in the process of instant claim 1. Further, Radhakrishnan does not teach or suggest use of an aqueous hydration media comprising ammonium sulphate and sucrose at 10 – 35 ml to hydrate each mmole of phospholipid without drug as recited in claim 1 because Radhakrishnan teaches 10-100ml of phosphate buffered saline/mmole of phospholipid (including EPG) having the drug in combination with lipids. See column 5, lines 5-29. There simply is no teaching, suggestion or motivation to look to Radhakrishnan for using such a volume of hydration as recited in instant claim 1 in order to achieve long circulation effect.

Uchiyama generally relates to the effects of the size and fluidity of liposomes on their accumulation in tumors. More importantly, Uchiyama discloses the use of 5 ml of phosphate buffered saline/mmole of phospholipid EPC or HEPC and dicetyl phosphate (DCP) in 5:1:4

molar ratio as a hydration medium. See section 2.2. The process of claim 1 recites an aqueous hydration media used in the range of 10 to 35 ml for each mmole of phospholipid present. The hydration medium is not simply a phosphate buffered saline but is, instead, comprised of ammonium sulfate and sucrose. Thus, Uchiyama does not teach or suggest using the volume of hydration media as recited in instant claim 1 in order to achieve long circulation effect.

Accordingly, Applicant respectfully submits that Forssen, Janoff, Radhakrishnan, and Uchiyama, alone or in combination, do not teach or suggest each and every element of the claims nor would one of ordinary skill in the art be motivated to even consider the amounts of the entirely different hydration medium taught by Radhakrishnan and Uchiyama. Thus, Applicant submits that the pending claims are patentable under 35 U.S.C § 103(a) and respectfully requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Hong/Janoff/Radhakrishnan/Uchiyama

The Examiner rejects claims 1-8, 10-22 and 61-62 under 35 U.S.C §103(a) as being unpatentable over Hong in view of Janoff and either Radhakrishnan or Uchiyama. The Examiner contends that to include sucrose in the hydration medium of Forssen would have been obvious to one of ordinary skill in the art since such a procedure would allegedly enable the presence of sucrose within the liposome as well as outside the liposome. The Examiner appears to rely on Hong for teaching a method of preparing doxorubicin loaded liposomes but admits that Hong does not teach the use of sucrose nor make clear the amount of hydration buffer added.

As evident in the title of Hong's paper, Hong is directed to the preparation of pegylated liposomes. Further evidence is found at page 3646, where Hong states:

> Small unilamellar vesicles (size < 100 nm) were prepared by a combination of the standard thin-film hydration method and repeated extrusion as described previously (17,18). Briefly, liposomes were composed of DSPC, cholesterol (3:2 molar ratio) with PEG-DSPE as indicated. Contents were hydrated at 55 °C in ammonium sulphate solution [250mM $(NH_4)_2SO_4$ (pH 5.0) 530 mOs] and extruded through polycarbonate membrane filters (Costar, Cambridge, MA) of 0.1 and 0.05 μm pore size using high pressure extrusion equipment (Lipex Biomembranes, Vancouver, British Columbia) at 55 °C. Doxorubicin was encapsulated by a remote loading method at a concentration of 1mg of doxorubicin per 10 μmole of phospholipid.

Thus, upon reading Hong, it becomes abundantly clear that Hong is directed to the preparation of pegylated liposomes. As previously explained, a process of preparation for pegylated liposomes does not obviously apply to non-pegylated liposomes. The Examiner cannot simply extract a single step from the Hong process and apply it to the process of making non-pegylated liposomes as recited in claim 1 without considering other steps. Applicants point out that there is simply no disclosure in the Hong reference that teaches or suggests how to make long circulating non-pegylated liposomes. Hong simply does not teach or suggest a process for the manufacture of long circulating non-pegylated liposomes as set forth in claim 1. Furthermore, no one would be motivated to even consider Hong for suggesting a non-pegylated liposome made by the process of claim 1. The Examiner has failed to provide any support or evidence to the contrary.

The Examiner further alleges that it would have been obvious to one of ordinary skill in the art to use the claimed amount of the hydration medium to hydrate the lipid of Forssen since Radhakrishnan and Uchiyama allegedly teach these are typical amounts of hydration medium. The propriety of the Examiner's position with regard to Radhakrishnan and Uchiyama is addressed above. For these same reasons, the Examiner's reliance on Radhakrishnan and Uchiyama is misplaced and any rejection based on Radhakrishnan and Uchiyama is improper. Thus, Applicant submits that the pending claims are patentable under 35 U.S.C § 103(a) and respectfully requests withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C § 103(a)-Hong/Janoff/Radhakrishnan/Uchiyama/Emanuel

The Examiner rejects claim 62 under 35 U.S.C §103(a) as being unpatentable over Hong in view of Janoff and either Radhakrishnan or Uchiyama, further in view of Emanuel.

As articulated above, Hong, Janoff, Radhakrishnan and Uchiyama alone or in combination, do not teach or suggest each and every element of the claims. Emanuel fails to cure the shortcomings of these references. Specifically, Emanuel fails to teach or suggest the sucrose-histidine buffer of claim 62. The Examiner has also failed to point to any motivation or suggestion that a person of ordinary skill would have even looked to Emanuel to accomplish a reduction in toxicity or increase in circulation time without any pegylated phospholipid as required by the pending claims.

Applicant respectfully requests withdrawal of this ground of rejection.

CONCLUSION

No additional fees are believed to be owed at this time. However, in the event that additional fees are required, the Commissioner is hereby authorized to charge Womble Carlyle Sandridge & Rice, PLLC Deposit Account No. 09-0528, or credit any overpayments to this account.

The Examiner is invited and encouraged to contact the undersigned at 703/394-2273 to discuss any matter in this application.

Respectfully submitted,
Womble Carlyle Sandridge & Rice, PLLC

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